UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,350	10/01/2003	Ursula Schindler	02481.1655-01	3812

22852 7590 06/27/2005

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 06/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/674,350	SCHINDLER ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,20,21 and 27-34* is/are rejected.

7)☒ Claim(s) *12-19 and 22-26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S. 0-3

FINAL ACTION

Applicant's amendment of 4-13-05 has been fully considered. While the amended claims 11, 20 and 21 have overcome the previous 102 rejection, they have raised new ground of rejection. The amended claims 30 and 33 have overcome the previous 112 rejections. However, applicant's argument has not overcome the previous 112 rejections for claim 29. Thus, the previous 112 rejections are maintained for claim 29 along with a new ground of rejection.

Claims 11-34 are pending.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 29 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation of "*activating at least one soluble guanylate cyclase*" does not have definite metes and bounds since it is not clear if a treatment or a bioassay is intended. Applicant argues "it is not necessary to specifically claim a treatment or bioassay." However, in the instant case, claim 29 can be interpreted as a treatment, which is an *in-vivo* process, or a bioassay, which can also be an *in-vitro* process. Depending on how claim 29 is interpreted, a reference may or may not be relevant. Thus, such a dilemma renders claim 29 indefinite.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Scope of Enablement:** Claim 29 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being **enabling** for the treatment of hypertension, stroke, angina pectoris, or myocardial infarct, does **not** reasonably provide **enable**ment for the treatment of other diseases that are allegedly related to guanylate cyclase such as: atherosclerosis, thrombosis, bronchial asthma, chronic renal insufficiency, diabetes, liver cirrhosis, etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

Claim 29 recites "A method for activating at least one soluble guanylate cyclase..." which is not specific to the treatment of any disease, but at the same time, encompasses the treatment of just about every disease known in the art because guanylate cyclase is an enzyme that is involved in virtually every cellular process. Also, said method is drawn to an *in-vitro* bioassay as well.

Therefore, the scope of claims 29 not only covers the treatment of a wide range of diseases (known and unknown presently), but also *in-vitro* bioassay which includes even diagnostic tests.

The amount of direction or guidance presented:

The specification only provides data for 14 compounds that can activate soluble guanylate cyclase. While such activity can warrant the treatment of hypertension, stroke, angina pectoris, or myocardial infarct, it does not have any correlation to the treatment of atherosclerosis, thrombosis, chronic renal insufficiency, diabetes, liver cirrhosis, improving learning capacity or memory power. Many of these diseases have underlying factors that are not related to guanylate cyclase, or they have additional factors. For example, atherosclerosis is caused by plagues of cholesterol, lipids, and cellular debris built up in the inner layer of the artery wall, thus, the most effective treatment is reducing such plaque. Clearly, activating guanylate cyclase would not treat atherosclerosis. Likewise, thrombosis is related to Factor X of

the blood coagulation pathway, and not related to guanylate cyclase. Similarly, diabetes is related to the availability of insulin, or the production of glycogen while chronic renal insufficiency and liver cirrhosis have other factors such as: alcohol consumption, hepatitis, and drug induced factor. Regarding improving learning capacity and memory power, there is nothing in the specification that would guide the skilled clinician to apply the claimed compounds for such a use.

Thus, merely showing the activation of guanylate cyclase for 14 compounds does not sufficiently guide the skilled clinician to practice the method recited the instant claim.

The state of the prior art:

Currently in the art, the drugs that treat hypertension, do not treat atherosclerosis while the cholesterol lowering agents can reduce atherosclerosis, but do not treat hypertension. Likewise, none of the anti-diabetic agents can treat hypertension, atherosclerosis, thrombosis, etc. In other words, there is no single agent that can treat the many diseases of different etiologies. Although activating guanylate cyclase would increase cGMP and could help in many conditions, as evident by the teaching of Lee et. al. (US'233), the activity of cGMP would mainly treat cardiovascular diseases such as: hypertension, stroke, angina pectoris, myocardial infarct, etc.

The relative skill of those in the art:

Even with the high level skill of those in the art such as physician and Ph. D., to treat the many diseases encompassed by the instant claims, one would have to carry out a

pharmacokinetic profile for each of the claimed compound, and establish a therapeutic index as well as LD_{50} for each of them. Such a task requires more than routine experimentation.

The predictability or unpredictability of the art and **the quantity of experimentation necessary**: It is well known that the pharmaceutical art is unpredictable because each disease manifests differently. Therefore, to treat the many diseases encompassed by the instant claim using a large number of compounds, it would require undue experimentation since no single agent can treat diseases of different etiologies.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 11, 20, 21 and 27-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Lee et. al.** (US 5,436,233 – cited previously). Although the above claims have been amended to exclude the species disclosed in US'233, other species and the generic teaching of US'233 can still render obvious the scope of said claims.

For example, the compound in Example 6(gg) (on column 60) would render obvious the compound of formula I wherein one of R^1 and R^2 is *$(C_1$-$C_8)$-alkyl substituted with hydroxyl*, and R^3 is a heteroaryl group. Likewise, the compounds in Examples 6(ss) and 6(tt) (on column 64) would render obvious the compound of formula I wherein one of R^1 and R^2 is *$(C_1$-$C_8)$-alkyl substituted with $(C_1$-$C_4)$-alkyl-$S(O)_m$*, and R^3 is a heteroaryl group.

The disclosed compounds differ from the claimed formula I by having a *quinazolinyl* ring, and not a *tetrahydroquinazolinyl* ring as claimed herein. However, the disclosed genus of formula (I) on column 4 allows for a *quinazolinyl* ring as well as a *tetrahydroquinazolinyl* ring with or without a substituent at the 5^{th}, 6^{th}, 7^{th} or 8^{th} position. Thus, said genus provides equivalent teaching for *quinazolinyl* and *tetrahydroquinazolinyl* rings.

The disclosed compounds can also increase cGMP by preventing it from being metabolized by cGMP-phosphodiesterase. Therefore, they can treat a number of diseases as recited in the method claims 29-34 (see column 1, lines 45-65 of US'233). Note, the method recited in claim 29 results in an increase cGMP, and thus would be obvious by the disclosed mechanism as well.

The process of claim 27 is also generically taught in Scheme A of US'233 since the term "comprising" does not exclude any starting materials, reaction conditions or steps.

With the generic and equivalent teachings provided, the skilled medicinal chemist would have been motivated to make and use tetrahydroquinazoline compounds of formula I having substituents cited above because said compounds would have been able to treat the same cardiovascular diseases as claimed herein.

Therefore, at the time that the invention was made, it would have been obvious to make and use some compounds claimed herein in view of the teaching of Lee et. al.

Claim Objections

4. Claims 12-19 and 22-26 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Said claims recite compounds having one of R^1 and R^2 as a *cycloalkyl* group, which is not taught in the prior arts of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

***

6-22-05

Tamthom N. Truong
Examiner
Art Unit 1624

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600